Accelerated Immunotherapy Schedules

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Disclosure

Consultant/Advisory Board:
Sanofi, Thermo Fisher Scientific

Speaker:
Mylan, Thermo Fisher Scientific

Honorarium:
Mylan, Sanofi, Thermo Fisher Scientific

Learning Objectives

- Upon completion of this session, participants should be able to:
  - Identify patients who would benefit from accelerated immunotherapy
  - Prescribe premedication for different types of accelerated immunotherapy
  - Safely give immunotherapy using an accelerated schedule

Two Phases of Allergen Immunotherapy

- Build-up Phase
  - Desensitization followed by tolerance and immunization
  - Increased risk of local and SR
  - No clinical improvement
- Maintenance Phase
  - Sustained injections to "fix" the immunization
  - Usually lasts 3-5 years

Build-up Schedules

- Traditional schedule
  - 1 injection per week
  - Maintenance achieved in 3-6 months.
- Cluster schedule
  - Several injections (2-3) in one day on non-consecutive days several days per week
  - Maintenance achieved in 4-8 weeks.
- Rush schedule
  - Increasing doses 15 to 60 minutes apart over 1 to 3 days until the target dose (usually slightly less than the maintenance dose) is achieved
  - The remainder of the build up phase proceeds using a traditional schedule until maintenance is achieved usually in less than 8 weeks.

Traditional Weekly Schedule

1:1000 (Green)	*1:100 (Blue)*	*1:10 (Yellow)*	*1:1 (Red)*
0.05 ml	0.05 ml	0.05 ml	0.05 ml
0.1 ml	0.1 ml	0.1 ml	0.1 ml
0.2 ml	0.2 ml	0.2 ml	0.15 ml
0.3 ml	0.3 ml	0.3 ml	0.2 ml
0.4 ml	0.4 ml	0.4 ml	0.25 ml
0.5 ml	0.5 ml	0.5 ml	0.3 ml
			0.35 ml
			0.4
			0.45 ml
			0.5 ml

Typical Cluster Schedule

Visit number	*Volume (ml)*	*Concentration*	*Color Vial*
1	0.1	1:1000	Green
	0.40	1:1000	Green
	0.1	1:100	Blue
2	0.20	1:100	Blue
	0.40	1:100	Blue
	0.07	1:10	Yellow
3	0.10	1:10	Yellow
	0.15	1:10	Yellow
	0.25	1:10	Yellow
4	0.35	1:10	Yellow
	0.5	1:10	Yellow
5	0.07	1:1	Red
	0.10	1:1	Red
6	0.15	1:1	Red
	0.20	1:1	Red
7	0.30	1:1	Red
	0.40	1:1	Red
8	0.50	1:1	Red

1-day RIT Schedule

Time (min)	*Volume (ml)*	*Dilution*	*Color Vial*
0	0.30	1:1,000	Green
30	0.10	1:100	Blue
60	0.30	1:100	Blue
90	0.05	1:10	Yellow
120	0.15	1:10	Yellow
180	0.30	1:10	Yellow
240	0.05	1:1	Red
300	0.10	1:1	Red

Sharkey, et al. Ann Allergy Asthma Immunol. 1996 Feb;76(2):175-80.

Another 1-day RIT Schedule

Time	*Volume (ml)*	*Dilution*	Color Vial
0	0.025	1:10,000	Silver
15	0.25	1:10,000	Silver
30	0.025	1:1,000	Green
45	0.25	1:1,000	Green
60	0.025	1:100	Blue
75	0.25	1:100	Blue
90	0.025	1:10	Yellow
105	0.1	1:10	Yellow

SR rate of 2% (18/893 patients) by stopping at the 1:10 dilution

Smits, et al. Allergy Asthma Proc. 2007 May-Jun;28(3):305-12

Venom Accelerated Schedule

Day	*Volume (ml)*	*Concentration (µg/ml)*	Dose, µg
1	0.05	1	0.05
1	0.1	1	0.1
1	0.2	1	0.2
1	0.4	1	0.4
1	0.8	1	0.8
1	0.2	10	2
1	0.5	10	5
1	1	10	10
1	0.2	100	20
1	0.2	100	20
2	0.2	100	20
2	0.3	100	30
2	0.5	100	50
3	1	100	100

Goldberg, et al. Ann Allergy Asthma Immunol. 2003 Oct;91(4):405-10

Venom Rush Immunotherapy

Time	Dose (µg)	*Time*	Dose (µg)
0	0.1	0	0.1
30	1	30	1
60	10	60	10
90	20	90	20
120	30	120	30
150	40	**150**	40

Schiavino , et al. Ann Allergy Asthma Immunol. 2004 Apr;92(4):409-13

Accelerated Schedules

- **Benefits**
  - Convenience (most common reason for discontinuing conventional immunotherapy)
  - Fewer office visits
  - Decreased cost
  - Improved compliance
  - More rapid onset of clinical benefit
  - Reduction of dosage errors (since maintenance is achieved much more rapidly as compared to traditional schedules)
  - Safety- the number of vials being used is reduced once a maintenance dose is reached
  - Reduction in vulnerable time between induction of increased IgE and IgG responses
- **Disadvantages**
  - Increased risk of systemic reactions (SR). This can be significantly decreased with the use of pre-medications.
  - Requires several injections on a single visit
  - Increased time and resources are needed in the health facility to give multiple injections

Candidates for accelerated schedules

- Difficulty reaching a maintenance dose on weekly immunotherapy due to systemic reactions or due to sub adherence
- Patients whose schedule precludes weekly injections for a prolonged time
- Asthmatics that cannot be adequately controlled but who can be controlled long enough to reach a maintenance dose with an accelerated schedule

Immunotherapy: Treatment Schedules

Conventional schedules

- Most commonly used: Injections given 1-2 times a week : Approximately 18-27 doses increments until maintenance dose is achieved
- Average build-up phase from 3-6 months
- Schedule may vary based on sensitivity
- Doses adjusted for exacerbations of symptoms and lapses in scheduled visits
- Patients should be evaluated every 6-12 months

Traditional Weekly Schedules

- The rate of SR using a traditional weekly schedule is 0.86% of injections or 28.6% of patients (1).
- Severe life threatening reactions occur in less than 1% (2).
- Fatalities occur at a rate of 1 out of every 2 million injections (3, 4).

1. J Allergy Clin Immunol. 1992 Oct;90(4 Pt 1):567-78
2. J Allergy Clin Immunol. 2011 Jan;127(1 Suppl):S1-55
3. J Allergy Clin Immunol. 2004 Jun;113(6):1129-36
4. J Allergy Clin Immunol. 1993 Jul;92(1 Pt 1):6-15

Rush Schedule

Time (minutes)	Volume (mL)	Dilution (v/v)	Vial Color	Dose (mg)	Cum Dose (mg)
0:00	0.30	1:1000	green	0.3	0.3
0:30	0.10	1:100	blue	1.0	1.3
1:00	0.30	1:100	blue	3.0	4.3
1:30	0.05	1:10	yellow	5.0	9.3
2:00	0.15	1:10	yellow	15.0	24.3
3:00	0.30	1:10	yellow	30.0	54.3
4:00	0.05	1:1	red	50.0	104.3
5:00	0.10	1:1	red	100.0	204.3
6:00	0.20	1:1	red	200.0	404.3

This should be followed by 8 weekly injections building up to and at the maintenance dose. The frequency can then be reduced to every 2 weeks.

Rush Immunotherapy: Early Experience

- 125 mite-sensitive asthmatics ages 4 to 57 years received RIT
- 43 (34.4%)had SRs.
- 35 had asthma and 8 had anaphylaxis
- Reaction rate per injection of 4.16%
- Predictors were:
  - Skin prick test end point sensitivity
  - FEV1 < 80%
- If the predicted patients had been excluded, SRs would have occurred 19.6% of the time
- Most SRs started within 15 minutes and none after 45 minutes
- No late onset SRs seen and only at doses > 0.5cc of 1:10,000

Bousquet, et al. J Allergy Clin Immunol. 1989;83,797-802

Premedication- RIT

- Sharkey, et al.
  - Multiple allergens as is typical in the United States
  - 2 day rush schedule
  - No premedication was given
  - 55% of patients had a SR
- Portnoy, et al.
  - Multiple allergens as is typical in the United States
  - 1 day rush schedule
  - astemizole, ranitidine and prednisone as pre-treatment
  - SRs in 73% in the placebo group vs 27% in the pre-medicated group

Sharkey, et al. Ann Allergy Asthma Immunol. 1996 Feb;76(2):175-80
Portnoy, et al. Ann Allergy. 1994 Nov;73(5):409-18

Schedule

Day	Date	Time	Volume	Dilution	PEFR	Rxn Grade
Day 1	_____	09:00	0.30 cc	1:100,000	_____	0 1 2 3 4 5 6
	_____	09:30	0.10 cc	1:10,000	_____	0 1 2 3 4 5 6
	_____	10:00	0.35 cc	1:10,000	_____	0 1 2 3 4 5 6
	_____	11:00	0.05 cc	1:1,000	_____	0 1 2 3 4 5 6
	_____	12:00	0.15 cc	1:1,000	_____	0 1 2 3 4 5 6
	_____	14:00	0.30 cc	1:1,000	_____	0 1 2 3 4 5 6
Day 2	_____	08:00	0.05 cc	1:100	_____	0 1 2 3 4 5 6
	_____	09:00	0.10 cc	1:100	_____	0 1 2 3 4 5 6
Week 1	_____	09:00	0.15 cc	1:100	_____	0 1 2 3 4 5 6

Portnoy et al. Ann Allergy. 1992 Jun;68(6):493-8.

Results

Pt.	LR	SR	Grade	Time to SR	Dose at SR	Completed RIT?	Subsequent Rxn?
AB	yes	no	0	n/a	n/a	yes	no
JL	no	no	0	n/a	n/a	yes	no
JM	no	no	0	n/a	n/a	yes	no
JA	no	no	0	n/a	n/a	yes	no
PB	yes	no	0	n/a	n/a	yes	no
SG	no	yes	3	90 min	0.1cc of 1:100	yes	no
NW	yes	yes	3	40 min	0.1cc of 1:100	yes	no
KW	no	yes	4	30 min	0.1cc of 1:100	yes	yes at 1 week
CB	no	yes	4	65 min	0.3cc of 1:1000	yes	no
JW	yes	yes	4	70 min	0.3cc of 1:1000	yes	yes at 4 weeks
TP	no	yes	5	60 min	0.3cc of 1:1000	no	yes at 2 weeks

(n/a=not applicable, SR=systemic reaction, LR=local reaction)

Portnoy et al. Ann Allergy. 1992 Jun;68(6):493-8.

Observations

- All but 1 patient achieved a "maintanence" dose
- LR's did not correlate with SR's
- Incidence of SR's was 55%
- SR's during RIT tend to occur greater than 60 minutes after the last injection
- None of the patients experienced late reactions (ie: after they went home)
- Patients with greater skin-sensitivity tended to react at lower concentrations of extract and with higher levels of SR

Portnoy et al. Ann Allergy. 1992 Jun;68(6):493-8.

Strategies to Reduce SRs

- Screen out patients with high skin test sensitivity
  - these may be the patients who need IT the most
  - how does one combine degree of skin test sensitivity with the number of antigens where there may be low sensitivity to each?
- Pretreatment (like with radiocontrast media)
  - not practical for conventional IT but is possible for RIT
  - does pretreating "mask" a SR that will occur later?
  - is the clinical efficacy as good if the patient is pretreated?
- Passive immunization with specific-IgG
  - not effective for venom RIT
  - did not effect the development of specific-IgG after RIT
- Stop at a lower dose (eg: 0.5mL of 1:10)

Strategies to Reduce Risks

- **Premedication**
  - Typically a corticosteroid, H1 and H2 blocker are prescribed to be taken 3 days prior to initiating rush immunotherapy (various specific pre-medication regimens have been described).
  - An H1 blocker alone is commonly used prior to cluster immunotherapy.
- **Selection of Patients**
  - $FEV_1 > 70\%$
  - Medically able to tolerate anaphylaxis
  - Medically able to tolerate treatment of anaphylaxis
  - Greater reaction on skin testing increases likelihood of SR

Premedication- Cluster

- Walker et al
  - grass allergen
  - 7 visits over a 4 week period
  - loratadine at least 15 min prior to cluster
  - 18% SR in pre-medicated group vs. 22% placebo.
- Ewbank et al
  - cat allergen
  - 8 visits over 4 weeks cluster schedule
  - loratadine 10 mg 2 hours prior to the procedure
  - no SR (no placebo group) using an

Walker, et al. J Allergy Clin Immunol. 2001 Jan;107(1):87-93
Eubank, et al. J Allergy Clin Immunol. 2003 Jan;111(1):155-61

Premedication- Cluster

- Nielsen et al
  - timothy and birch
  - 7 weekly visit cluster schedule.
  - loratadine 2 hours before injection
  - placebo had 79.2% SR compared with 33.3% in the pre-medicated group
- Nanda et al
  - cat allergen
  - schedule of 8 visits over 4 weeks
  - pre-medication with zafirlukast and loratadine (no placebo group)
  - 1 out of 26 patients had SR

Nielsen, et al. J Allergy Clin Immunol. 1996 Jun;97(6):1207-13.
Nanda, et al. J Allergy Clin Immunol. 2004 Dec;114(6):1339-44

Premedication (Controlled Study)

- Active Group- Opaque gelatin capsules with:
  - Astemizole: 3 tabs day 1, 2 tabs day 2, 1 tab day 2
  - Ranitadine: 1 tab BID for 3 days
  - Prednisone: 30mg BID for 3 days
- Placebo Group- Opaque gelatin capsules with:
  - lactose

Portnoy J, et al. Ann Allergy. 1994 Nov;73(5):409-18.

Results

Characteristic	Placebo (N=11)	Active (N=11)	p-value
Reaction Grade±SEM	3.0±0.5	1.3±0.6	0.038
No. with SR	8 (73%)	3 (27%)	0.047
No. with LR	8 (73%)	3 (27%)	0.047
No. Completing RIT	7 (64%)	10 (91%)	0.311
Wheal±SEM	3.4±1.0	1.4±0.8	0.148
Erythema±SEM	12.9±3.9	2.0±1.7	0.030

Portnoy J, et al. Ann Allergy. 1994 Nov;73(5):409-18.

Patients with SRs

Group	Disease	LR?	SR Grade	Time to SR	Dose at SR	Step
Placebo	Both	No	5	100	0.15cc of 1:10	5
Placebo	Both	Yes	5	120	0.15cc of 1:10	5
Placebo	Both	Yes	4	30	0.05cc of 1:1	7
Placebo	Both	Yes	5	35	0.05cc of 1:10	4
Placebo	Both	Yes	4	30	0.10cc of 1:1	8
Placebo	Both	Yes	2	45	0.10cc of 1:1	8
Placebo	Rhinitis	No	3	115	0.15cc of 1:10	5
Placebo	Both	Yes	3	40	0.30cc of 1:10	6
Active	Both	No	3	95	0.10cc of 1:1	8
Active	Both	No	4	20	0.30cc of 1:10	6
Active	Rhinitis	yes	5	60	0.30cc of 1:10	6
				Mean=62.7±11.3	Median=6.0	

Portnoy J, et al. Ann Allergy. 1994 Nov;73(5):409-18.

Predictors of SRs

Predictor	p-value
Erythema (pre-Rx)	**<.001**
Erythema (on Rx)	**.030**
Wheal (pre-Rx)	**<.001**
Wheal (on Rx)	**.148**
Age	**.287**
FEV1	**.995**
Sex	**.080**
Race	**.670**
Rx Group	**.047**
No. Antigens	**.823**

Portnoy J, et al. Ann Allergy. 1994 Nov;73(5):409-18.

- 10/11 active and 7/11 placebo patients were able to reach “maintanence” (p=0.173)
- Reactions tended to occur 1-2 hours after the last injection
- Only 1 patient (placebo group) had a SR during the following 8 weeks with subsequent injections

Portnoy J, et al. Ann Allergy. 1994 Nov;73(5):409-18.

Premedication- RIT

- Harvey et al.
  - review of 65 patients pre-medicated with prednisone, cetirizine, ranitidine and either montelukast or zafirlukast.
  - Used the Portnoy/Sharkey 1 day rush schedule
  - SR occurred in 38%.
  - 4 patients required epinephrine and 1 patient had a reaction graded as severe
- Casale et al.
  - used ragweed.
  - Pre-medication with fexofenadine and omalizumab or placebo for 9 weeks.
  - SR in 25.6% of placebo group vs. 5.6% ofthe omalizumab group

Harvey, et al. Ann Allergy Asthma Immunol. 2004 Apr;92(4):414-9
Casale, et al. J Allergy Clin Immunol. 2006 Jan;117(1):134-40

Premedication- RIT

- Hejjaoui et al.
  - Used a 3-day rush schedule
  - Premed with methylprednisolone, ketotifen and theophylline
  - For dust mite: 36% had a SR using a 3 day schedule without premedication and 16% with premedication.
  - This decreased to 7.3% when excluding patients with FEV-1 < 70 % and slowing the rate with large local reactions greater than 10 cm.
  - SR decreased to 5.4% when using a “step protocol” using 9 injections administered in 6 visits over 2 weeks.
  - Results were similar with pollen extracts.

Hejjaoui, et al. Allergy Clin Immunol. 1990 Feb;85(2):473-9

Procedure - 1 Day RIT

- The Patient
  - Another adult ideally should be present.
  - should have signed informed consent.
  - should have taken pre-medication as prescribed.
- The clinic staff
  - trained in administering RIT
  - able to provide close monitoring
  - comfortable with the treatment of anaphylaxis.

Equipment & Supplies – RIT

- The patient's allergy extract
- injection supplies (syringe, alcohol wipes)
- peak flow meter, spirometry
- IV supplies
- blood pressure cuff and stethoscope, thermometer
- RIT forms, emergency equipment (pre-drawn epinephrine and albuterol with nebulizer).
- dosing guide at the patient's bedside with pre-calculated doses of all anticipated emergency medications based on the patient's weight and reviewed by at least 2 health professionals.

Pre-treatment – RIT

- Discuss the purpose and procedure of RIT and informed consent is signed.
- Discuss epinephrine and its use if needed.
- The teaching record is signed.
- The family receives prescriptions for pre-medication (corticosteroid, H1 and H2 blockers, possibly LTM) and for an epinephrine autoinjector to take home after the injections are done.

Premedication

- ***Cluster Immunotherapy:***
  - Consider the patient taking an H1 and H2 antagonist on injection days
    - there is no evidence that doing so reduces the likelihood or severity of a local or systemic reaction.
- ***Rush Immunotherapy:***
  Start prophylaxis medication 2 days prior to the procedure
  - H-1 antagonist
  - H-2 antagonist
  - Corticosteroid
  - Possibly a leukotriene receptor antagonist

RIT - Treatment Day

- The nurse takes baseline vital signs
- The nurse obtains a height, weight and baseline pulmonary function test
- The nurse starts a heparin lock (this is controversial and is not always done)
- The physician examines the patient
- Consider skin prick testing prior to beginning immunotherapy. Large reactions may imply a higher likelihood for SR and/or a failure to comply with the pre-treatment medications. (1)
- The physician begins the immunotherapy as scheduled on the RIT forms. Peak flow readings are obtained before and thirty minutes after each injection.

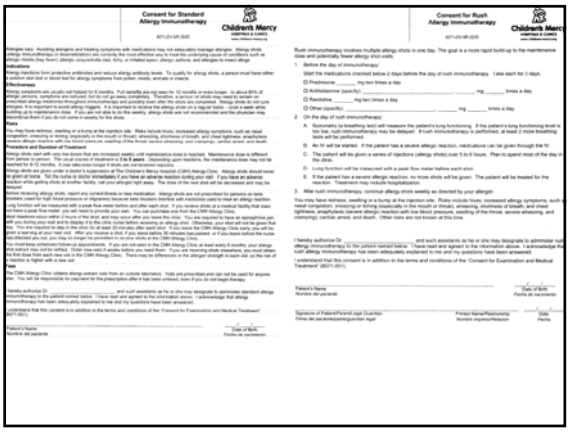
1. Ann Allergy. 1994 Nov;73(5):409-18.

RIT - Treatment Day

- The patient is carefully monitored for signs of local and systemic reactions.
- The allergy shot schedule is continued if no reactions occur. If a reaction occurs and is only local the patient can be treated as necessary. The procedure may continue if the reaction resolves.
- Follow up vital signs and pulmonary function tests are done as needed throughout the procedure.
- The patient is observed for at least 2 hours after the final injection.
- The patient is discharged with follow up instructions to return in one week for next injection.

Considerations

- Consider stopping injections if a large local reaction develops or evidence of a systemic reaction.
- For extremely sensitive individuals it may be desirable to stop giving injections after the 1:10 (v/v) vial to avoid inducing a systemic reaction.
- Patients should be observed for at least 2 hours after the last injection during the rush day.
- The patient must return within 1 week for subsequent injections. Otherwise there is an increased risk of a SR.

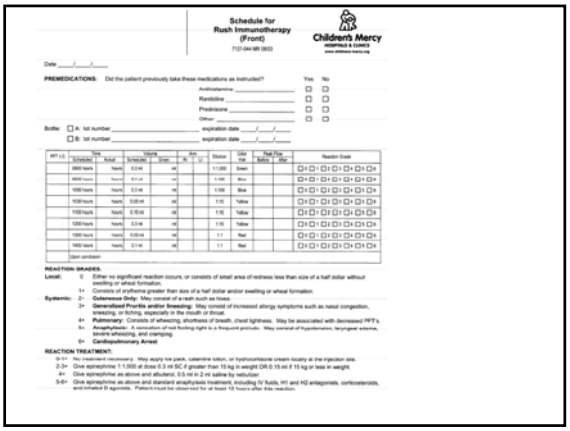


Consent for Standard Allergy Immunotherapy

Children's Mercy HOSPITALS & CLINICS

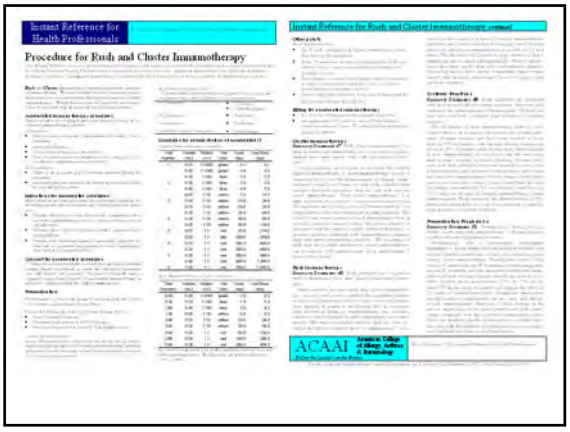
Consent for Rush Allergy Immunotherapy

Children's Mercy HOSPITALS & CLINICS



Schedule for Rush Immunotherapy (Front)

Children's Mercy HOSPITALS & CLINICS



Instant Reference for Health Professionals

Procedure for Rush and Cluster Immunotherapy

Instant Reference for Rush and Cluster Immunotherapy continued

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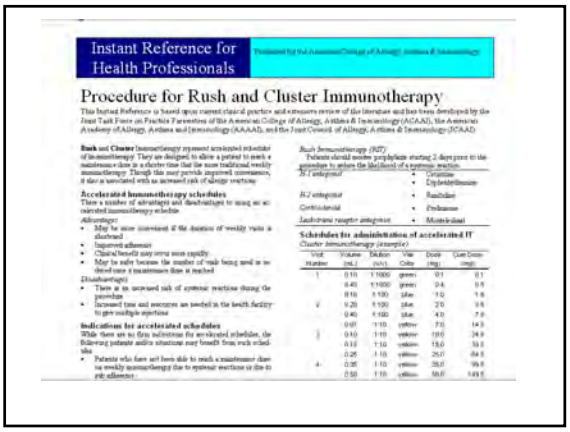
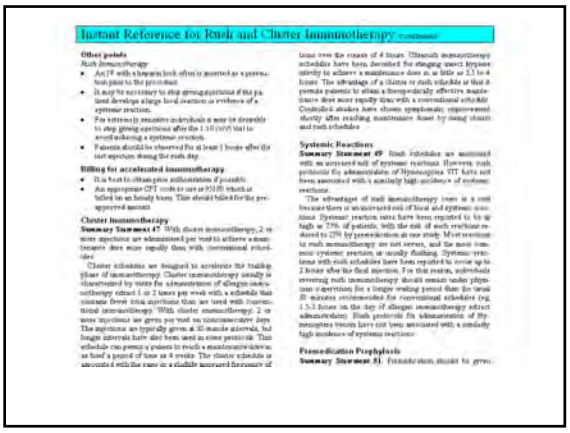


Instant Reference for Health Professionals

Procedure for Rush and Cluster Immunotherapy



Instant Reference for Rush and Cluster Immunotherapy (continued)